

### REMARKS

The Office Action has been carefully reviewed and the following remarks are made in light of the Office Action:

Independent claim 1 has been canceled and replaced by the newly added independent claim 29 and dependent claims 30-31. Step (iii) of new claim 29 refers to screening for peptides exhibiting such “target” biological activity. Support for this amendment can be found, for example, at page 6, line 22. New claim 29 also specifies that the assay used to screen for such “target” biological activity is selected from the group consisting of “biochemical-based assays” and “cell-based assays.” Support for this amendment can be found, for example, in present claim 22 as well as at page 14, lines 10-12.

Claims 2-5, 9, 15-20, 25 and 27, which previously referred to claim 1, have been newly amended so that now they refer to the newly added independent claim 29.

Claims 10-14, 22 and 28 have been canceled.

Claims 18-21 and 27, which previously referred to “said biological activity”, have been newly amended so that now they refer to “said target biological activity”.

Claims 23-24, which previously referred to claim 22, have been newly amended so that now they refer to the newly added independent claim 29.

Claims 25-26, which previously referred to “said fractionation of step (iii) and/or step (v)”, have been newly amended so that now they refer to “said fractionation of step (ii)”.

No new matter has been entered as a result of any of these amendments.

Therefore, claims 2-9, 15-21, 23-27 and 29-31 are presently under examination. Entry and consideration of the foregoing amendments is respectfully requested.

## RESPONSE

### Double Patenting

Claims 12-13 are rejected under 37 CFR 1.75, as allegedly being a substantial duplicate thereof. Applicant has hereby canceled claims 12-13, and the rejection is therefore moot.

### Claims Rejections – 35 U.S.C. § 112, second paragraph

Claims 1-28 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has hereby canceled claim 1, and replaced by new claims 29-31 which no longer include the phrase “optionally”. The optional steps in claim 1 are now presented as further steps in the new claim 30. In addition, new claim 29 now specifically recites that the screening in step (iii) is carried out using an assay which screens for the one or more target biological activities and is selected from the group consisting of biochemical-based assays and cell-based assays, the latter feature being recited in present claim 22.

In addition, applicant hereby canceled claims 10-14, 22 and 28, and the rejection is therefore moot as regards these claims. All of the remaining claims depend either directly or indirectly from new claim 29. The Examiner is respectfully requested to withdraw this rejection in view of the claim amendments.

### Claims Rejections – 35 U.S.C. § 102 and 35 U.S.C. § 103

Claims 1-2, 4, 9-10, 14-21 and 25-28 are rejected under 35 U.S.C. § 102 (b), as allegedly being anticipated by Jindal *et al* (US Patent No. 6,358,692). In addition, claims 3, 5-8, 11-13 and

22-24 are rejected under 35 U.S.C. § 103 (a), as allegedly being unpatentable over Jindal *et al* (US Patent No. 6,358,692) as the primary reference.

Before considering the cited document in detail, Applicant respectfully points out that the specification discloses that the present invention is based on the premise that controlled proteolytic digestion of naturally occurring proteins will result in the liberation of "cryptic bioactive peptides that ordinarily lie hidden within intact and folded proteins" (see page 2, line 23 to page 3, line 4). Thus, the present invention provides a method including systematic generation of peptide libraries (for example by enzymatic or chemical cleavage or physical digestion) under controlled digestion conditions to provide a library of peptides which may comprise partial, intermediate and/or complete digestion of the initial protein source, thus providing a comprehensive range of protein fragments (page 11, lines 2 to 4). This systematic approach to the production of a library of peptides enables the production of a comprehensive set of peptides which greatly enhances the possibility of unmasking or liberating "cryptic" biologically active peptides that would ordinarily be hidden within the intact protein source.

The method of the present invention includes screening steps in which the library, or separated fractions or sub-fractions thereof, are screened to identify in the library, fractions or sub-fractions, peptides exhibiting one or more "target" biological activities. These screening steps are carried out by bioassays, preferably high throughput, automated screening assays, to identify potential bioactivities with relevance to major therapeutic applications. As described at page 14, lines 9 to 19 of the specification, the bioassays include a wide array of both biochemical and cell-based assays which screen for agonist or antagonist activity. In other words, the step of screening the library, fractions or sub-fractions is directed to identifying peptides which exhibit one or more functional, target biological activities.

It is also important to note that the screening assays used in the present invention are directed towards directly identifying functional target biological activities without requiring any prior knowledge of a pre-selected binding target or ligand. The method of the invention does not therefore require the identification of a pre-selected target molecule at the outset of the screening process. In the present invention the target biological activity is often associated with a very complex structure such as a cell and the result of the screening assay is not simply the binding to a predetermined target molecule but is rather a true "biological" activity, for example agonist or antagonist activity in a biological system, such as platelet activation. For instance, in Example I of the present application an assay system is described for the identification of peptides which may be used for assessing platelet activation based on the phenomenon that platelet activation results in a substantial release of ATP which may be quantified. It is important to appreciate that a particular library may be shown to inhibit platelet activation in such an assay through interaction with one of several molecular targets known to modulate platelet activity including receptors for collagen, ADP, thrombin, prostacyclin, thromboxane A2, adhesive receptors and aggregation receptors such as GPIIb/IIIa. Indeed, such peptides may act through as yet undefined mechanisms. Thus, the use of a cell-based or biochemical-based assay such as platelet activation does not imply a single biological target. This approach enhances the possibility of identifying "cryptic" biologically active peptides that would not be identified simply through assay for binding to a particular ligand.

Applicant hereby respectfully explains in detail below that Jindal *et al* neither discloses nor suggests a method for the detection of bioactive peptides exhibiting a target biological activity in accordance with the present invention. The key difference is that Jindal *et al* is concerned with analyzing binding affinities to a particular target such as an antibody raised

against a particular protein, whereas the present invention is concerned with identifying a true biological activity (such as agonist or antagonist activity) in a biological system. Accordingly, the "target" is a "target biological activity" not a target such as an antibody raised against a particular protein. Thus, the amendments now proposed, particularly in new claim 29, emphasize that the present invention does not identify binding to a particular target, but rather involves identifying peptides exhibiting "target biological activities".

Jindal *et al* discloses a method for screening a sample to select a ligand to a target of interest on the basis of one or more binding characteristics. Thus, the method disclosed in this document is based on identification of ligands with specific binding activity for a particular target of interest which is pre-selected and requires a pre-selected target of interest in order to identify a candidate ligand. Such ligand binding does not necessarily translate to functional bioactivity, and it is well known that only a small fraction of binding ligands have functional activity. Thus, a ligand selected by the method of Jindal *et al* does not necessarily correspond to a molecule having physiologically relevant, "functional" activity. In contrast, the presently claimed invention is directed towards directly identifying functional target bioactivity, without any prior knowledge or requirement of a pre-selected target of interest, and in fact independent of any pre-selected target of interest.

Jindal *et al* itself emphasizes the distinction between use of screening assays directed towards identifying biological activity and the ligand/target binding affinity approach of Jindal *et al*. In fact, this document at column 2, lines 4-8 explicitly states that screening of suitable peptide libraries "frequently is performed either by immunoassay or by laboriously assaying for a particular biological function (e.g. blocking of viral replication)", pointing out that these methods "are not necessarily target based and in most cases involved tedious set up". Thus, this document

describes these screening methods directed towards identifying functional biological activity as "not entirely satisfactory" (see column 2, lines 37 to 38). That would clearly not lead a person skilled in the art towards the invention. The specific reference to the use of screening assays which are biochemical-based assays and cell-based assays in amended claim 29 clearly differentiates from the screening method of Jindal *et al* which utilizes ligand-target binding interaction. Jindal *et al* chooses a single protein target to be screened for binding partners (rHsp70 in Fig. 6 and 7 and concanavalin A in Fig. 8). In contrast, the invention does not rely on interaction with a single biological target. Jindal *et al* therefore does not disclose a method for the detection of bioactive peptides using screening assays to identify target biological activities which are biochemical-based or cell-based assays. Nor, without the benefit of hindsight, would a person skilled in the art be led to such a method from the disclosure of Jindal *et al*. If anything, Jindal *et al* clearly teaches away from the use of screening assays for a functional target biological activity which are embodied in the method of the present invention.

Accordingly, since this cited document does not disclose or teach a method which embodies screening assays to identify a functional target biological activity, and in fact focuses solely on screening to identify a ligand binding to a pre-selected target of interest, the method for screening a peptide library for bioactive peptides which is provided by the present invention is therefore not anticipated by the disclosure of the cited reference. Therefore, the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. § 102 (b) and issue the pending claims.

Furthermore, none of the secondary references relied on by the Examiner in the rejection under 35 U.S.C. § 103 (a) addresses the deficiency in the teaching of Jindal *et al* as outlined above or provides any disclosure or teaching which, even if combined with the teaching of Jindal

*et al*, would provide a method for screening a peptide library for bioactive peptides as recited in the amended claims, particularly new claim 29. Therefore, the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. § 103 (a) and issue the pending claims.

### CONCLUSION

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application and, therefore, requests an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

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COOLEY GODWARD KRONISH LLP  
ATTN: Patent Group  
777 6<sup>th</sup> Street NW, Suite 1100  
Washington, DC 20001

Tel: (202) 842-7800  
Fax: (202) 842-7899

Respectfully submitted,  
COOLEY GODWARD KRONISH LLP

By:

Erich E. Veitenheimer  
Erich E. Veitenheimer, Ph.D  
Reg. No. 40,420